# The Effect of the Level of Micromixing on the Optimal Design of CSTR's Performing Michaëlis–Menten Reactions

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An analytical formula for the calculation of the substrate conversion under complete segregation conditions in a CSTR performing a biochemical reaction following Michaëlis–Menten kinetics is obtained. The errors on the expected conversion arising from using an optimal reactor design based on the assumption of complete micromixing conditions are discussed. Methods for the determination of the optimal reactor size profile for a series of CSTR's under complete segregation conditions are reported, using the minimum of the overall space time as the objective function.

On a obtenu une formule analytique pour le calcul de la conversion du substrat dans des conditions de ségrégation complète dans un réacteur agité continu dans lequel se produit une réaction biochimique selon la cinétique de Michaëlis–Menten. On a analysé les erreurs sur la conversion théorique causées par l'hypothèse d'un micro-mélange complet ayant servi à la conception du réacteur. On présente des méthodes pour la détermination du profil de taille du réacteur optimal pour une série de réacteurs agités continus dans des conditions de ségrégation complète, qui utilisent comme fonction objectif le minimum de l'espace temps global.

Keywords: micromixing state, complete segregation, Michaëlis–Menten kinetics, optimal CSTR's in series.

Enzymes are remarkable catalysts in three major aspects: activity, specificity, and versatility. These characteristics have emphasized their industrial application for the catalysis of a great number of reactions within the food, medical, and cleaning fields (Arima, 1964).

Considerable attention has been given to reactor systems consisting of a series of continuous stirred tank reactors (CSTR's) due to the simplicity of the required analysis and the great practical importance of such systems. Besides the lower construction costs when compared to classical tubular reactors, the efficient stirring of the reactor content ensures uniform temperature (thus avoiding local hot spots), coupled with ease of access to the interior surface for maintenance, and appreciable residence times (Hill, 1977). In standard textbooks on chemical reaction engineering such as Aris (1961) and Levenspiel (1972) general concepts of reactor design and optimization for $n$-th order reaction kinetics are referred to, whereas Bischoff (1966) covered the field of biochemical reactions such as the Monod equation for fermentation devices. Luyben and Tramper (1982) proved that the minimum overall space time through a series of CSTR's where a single-substrate, Michaëlis–Menten reaction takes place is obtained when a simple recursive relation involving the substrate concentrations at each three consecutive streams applies. Their derivation assumed a state of maximum mixedness. Malcata (1988) reported a similar mathematical procedure leading to the optimization of the size of a series of CSTR's performing Ping-Pong enzymatic reactions; later his reasoning was applied to the case of allosteric enzymes performing single substrate biochemical reactions (Malcata, 1989b). The foregoing analyses have been extended in order to include optimization criteria based on scale-up factors for the equipment cost with respect to the size larger than unity (Malcata, 1989a). Bailey and Ollis (1986) considered a half-order irreversible reaction ocurring in a CSTR as an approximation to the Michaëlis–Menten form for a narrow range of substrate concentrations close to the kinetic constant, and reported an expression for the conversion under complete segregation. Malcata (1987) developed computer software able to numerically compute the limits of conversion for complete segregation and maximum mixedness conditions for a biochemical reaction with any given kinetic equation that takes place in a reactor with a known residence time distribution.

This Note deals with the development of a theoretical analysis for the optimal design of isothermal CSTR's in series performing a single-substrate, Michaëlis–Menten reaction. The minimisation of the overall space time through the reactor network is used as the objective function, realizing that other criteria could have been used. The effect of the state of micromixing on the conversion of substrate is discussed, and iterative procedures leading to the calculation of the optimum intermediate concentrations under complete segregation are presented.

## Theoretical analysis

Consider $N$ continuous stirred tank reactors in series where an enzyme catalysed reaction takes place in the liquid phase. If the single-substrate, Michaëlis–Menten kinetics is used to model the reaction system, and if maximum mixedness occurs within the reacting phase (Zwietering, 1959), then the material balance for the substrate in reactor $i$ can be written as

$$Da_i = \frac{[C^*_{i-1} - C^*_{i,cm}]\,[K^* + C^*_{i,cm}]}{C^*_{i,cm}}\,;\; i = 1,2,\ldots, N \qquad \ldots\ldots\ldots\

The minimum overall space time through the reactor network can be obtained from Equation (2) by setting all the derivatives equal to zero (Malcata, 1989b) and is equivalent to the following condition:

$$C^*_{i,cm,opt}{}^2 = C^*_{i-1,cm} C^*_{1+1,cm} \quad \ldots\ldots (3)$$

The foregoing formulae were derived on the assumption that the stirring of the fluid is very efficient so that concentration gradients on the molecular level are not allowed to build up inside the reactors.

The other limiting situation assumes no interchange between fluid elements moving through the reactor as if they were flowing through ideal plug flow reactors (Villermaux, 1976). In the latter case the conversion can be calculated from (Levenspiel, 1972):

$$C^*_{i,cs} = \int_0^\infty E^*_i(\xi)\, C^*_{pf}(\xi)\, d\xi \quad \ldots\ldots (4)$$

The residence time distribution density function for the $i$-th CSTR can be defined as follows (Hill, 1977):

$$E^*_i(t^*) = \exp\{-t^*\} \quad \ldots\ldots (5)$$

where the symbols are again defined in the Nomenclature. The material balance of the substrate in a plug flow reactor with arbitrary space time using Michaëlis–Menten kinetics is given by

$$\frac{dC^*_{pf}}{d\sigma} = -\frac{Da_{pf} C^*_{pf}}{K^* + C^*_{pf}} \quad \ldots\ldots (6)$$

Integration of Equation (6) using the initial condition

$$@\sigma = 0,\ C^*_{pf} = 1 \quad \ldots\ldots (7)$$

yields

$$\sigma = \frac{1 - C^*_{pf} - K^* ln\{C^*_{pf}\}}{Da_{pf}} \quad \ldots\ldots (8)$$

Equation (8) cannot be used to obtain $C^*_{pf}$ as an explicit function of $\sigma$. An appropriate way to overcome this difficulty is defining a new dummy variable of integration in Equation (4) with the aid of Equation (6) according to

$$d\xi := -\frac{K^* + \zeta}{Da_i\, \zeta}\, d\zeta \quad \ldots\ldots (9)$$

together with the initial and final conditions

$$@\xi = 0,\ \zeta = 1 \quad \ldots\ldots (10)$$

and

$$as\ \xi \to \infty,\ \zeta \to 0 \quad \ldots\ldots (11)$$

respectively. Using Equations (5) and (9)–(11) in Equation (4), and performing a preliminary step of integration by parts, one obtains

$$C^*_{i,cs} = C^*_{i-1,cs} - C^{*\,-K^*/Da_i}_{i-1,cs} \exp\{-C^*_{i-1,cs}/Da_i\} \int_0^{C^*_{i-1,cs}} \zeta^{-K^*/Da_i} \exp\{\zeta/Da_i\}\, d\zeta \quad \ldots\ldots (12)$$

The remaining integration may now proceed, after expansion of the integrating function as a MacLaurin series (Stephenson, 1973), to give

$$C^*_{i,cs} = C^*_{i-1,cs} - \exp\{-C^*_{i-1,cs}/Da_i\} \sum_{n=0}^{\infty} \frac{C^{*\,n+1}_{i-1,cs}}{\left(n + 1 + \dfrac{K^*}{Da_i}\right) Da_i^n\, n!} \quad \ldots\ldots (13)$$

Since an infinite series of positive terms results, d'Alembert's ratio test (Stephenson, 1973) may be used to prove that the right hand side of Equation (13) converges for all finite values of parameters $K^*$ and $Da_i$.

If the exponential term preceding the summation in Equation (13) is in turn expanded as a MacLaurin series, and if each term of the resulting series is multiplied by all terms of the second series, the following result is obtained

$$C^*_{i,cs} = C^*_{i-1,cs}\left[1 - \Gamma\left\{1 + \frac{K^*}{Da_i}\right\} \sum_{n=0}^{\infty} \frac{(-1)^n\, C^{*\,n}_{i-1,cs}}{Da_i^n\, \Gamma\left\{n + 2 + \dfrac{K^*}{Da_i}\right\}}\right] \quad \ldots\ldots (14)$$

Since the radius of convergence of the power series resulting from the expansion of a simple exponential function is infinity (Spiegel, 1968), Cauchy's theorem for the product of two infinite power series can be used to ensure absolute convergence of the right hand side of Equation (14) over the whole real range (Kreyszig, 1979). The convergence of the series implies that the absolute values of the terms decrease as $n$ increases. Since the terms are alternatively positive and negative, the absolute value of the first term discarded is an upper bound for the truncation error. This argument is useful if an *a priori* estimate of the number of terms required for a given fractional error is desired. For the case where $K^*/Da_i$ is large compared to $n + 1$, one obtains

$$n_{max,1\%,K^*/Da_i \to \infty} = \sum_{m=0}^{\infty} H\left\{\frac{ln\{K^* Er/Da_i\}}{ln\{C^*_{i-1,cs}/K^*\}} - m\right\} - 1 \quad \ldots\ldots (15)$$

If, on the other hand, $K^*/Da_i$ is small compared to $n + 1$, then Stirling's asymptotic approximation (Beyer, 1978) and the truncated expansion of $ln\{n + 1\}$ as $4n/(2 + n)$ can be used for up to $n = 50$ in order to obtain

$$\left(ln\left(\frac{C^*_{i-1,cs}}{Da_i}\right) - 3\right)(n_{max,1\%,K^*/Da_i \to 0})^2 + \left(2\, ln\left(\frac{C^*_{i-1,cs}}{Da_i}\right) - \frac{ln(2\pi)}{2} - ln(Er) - 3\right) n_{max,1\%\,K^*/Da_i \to 0} - (ln(2\pi) + 2(ln(Er) - 1)) = 0 \quad \ldots\ldots (16)$$

Solving Equation (16), one obtains $n_{max,1\%,K^*/Da_i \to 0}$ as the largest integer that does not exceed the greater root. Appropriate values for $Er$ are of the order of $10^{-2}$.

When parameter $K^*$ approaches zero Equation (13) tends asymptotically to

$$C^*_{i,cs,K^* \to 0} = C^*_{i-1,cs} - Da_i \left(1 - \exp\left(-\frac{C^*_{i-1,cs}}{Da_i}\right)\right) \quad \ldots\ldots (17)$$

The limits of this behavior with varying $Da_i$ are, therefore, given by

$$\lim C^*_{i,cs,K^* \to 0} = C^*_{i-1,cs} - Da_i \quad Da_i \to 0 \quad \ldots\ldots (18)$$

and

$$\lim C^*_{i,cs,K^* \to 0} = \frac{1}{2} C^*_{i-1,cs} \left(1 - \exp\left(-\frac{C^*_{i-1,cs}}{Da_i}\right)\right) \quad Da_i \to \infty \quad \ldots\ldots (19)$$

When parameter $K^*$ tends to infinity Equation (13) reduces to

$$C^*_{i,cs,K^* \to \infty} = \frac{C^*_{i-1,cs}}{1 + \frac{Da_i}{K^*}} \quad \ldots\ldots (20)$$

The limits of this behavior are, thus,

$$\lim C^*_{i,cs,K^* \to \infty} = C^*_{i-1,cs} \quad Da_i \to 0 \quad \ldots\ldots (21)$$

and

$$\lim C^*_{i,cs,K^* \to \infty} = \frac{K^* C^*_{i-1,cs}}{Da_i} \quad Da_i \to \infty \quad \ldots\ldots (22)$$

Furthermore, the derivative of $C^*_{i,cs}$ with respect to $Da_i$ can be obtained from Equation (13) to be

$$\left\{\frac{\partial C^*_{i,cs}}{\partial Da_i}\right\}_{C^*_{i-1,cs}} = -\frac{\exp\left(-\frac{C^*_{i-1,cs}}{Da_i}\right)}{Da_i^2} \sum_{n=0}^{\infty} \frac{C^{*\,n+1}_{i-1,cs}}{\left(n + 1 + \frac{K^*}{Da_i}\right) Da_i^n n!} \left(\frac{K^*}{n + 1 + \frac{K^*}{Da_i}} + \frac{C^*_{i-1,cs}}{n + 2 + \frac{K^*}{Da_i}}\right) \quad \ldots\ldots (23)$$

Combining Equations (2) and (23), one eventually obtains the rate of variation of $C^*_{i,cs}$ with $C^*_{i,cm}$. Equation (14) was combined with Equation (1) for a number of values for parameter $K^*$ to give the graphical plot denoted as Figure 1. The dimensionless concentrations of the outlet streams of each reactor in a series of CSTR's under the assumption of complete segregation and complete micromixing are

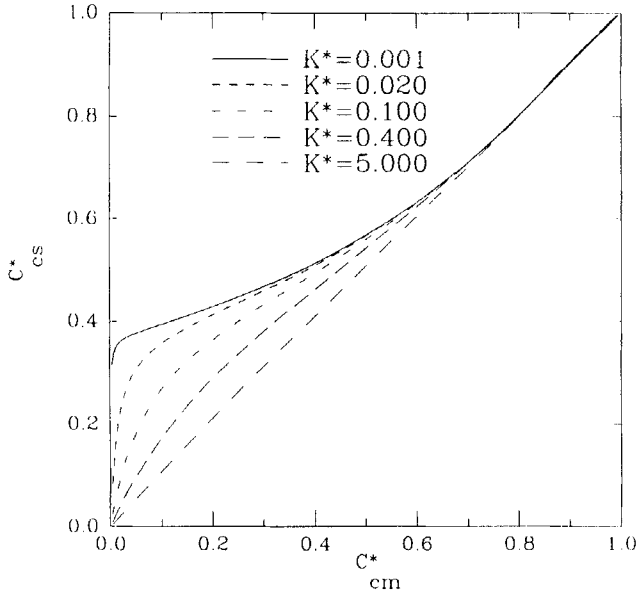


Figure 1 — Normalized substrate concentration under the assumption of complete segregation, $C^*_{cs}$, as a function of the normalized substrate concentration under the assumption of complete micromixing, $C^*_{cm}$, for the outlet stream of a single CSTR using a number of values for the dimensionless kinetic parameter $K^*$.

tabulated in Tables 1 and 2 for the case of $K^*$ equal to $10^{-2}$ and $10^{-1}$, respectively. It was assumed in these tables that the size of each CSTR was obtained from Equations (1) and (3), respectively, which were derived under the assumption of complete micromixing.

The analytical condition leading to Equation (3),

$$\left\{\frac{\partial Da_{tot}}{\partial C^*_{i,cm}}\right\}_{C^*_N} = 0 \quad \ldots\ldots (24)$$

can assume the following equivalent, yet more convenient form,

$$\left\{\frac{\partial Da_{tot}}{\partial Da_{i,cs}}\right\}_{C^*_N} = 0 \quad \ldots\ldots (25)$$

for the case of total segregation. If the $N$ CSTR's are considered at the same time, Equation (4) becomes

$$\Phi := \int_0^\infty E^{**}_{tot}(\omega)\, C^*_{pf}(\omega)\, d\omega - C^*_{N,cs} = 0 \quad \ldots\ldots (26)$$

The residence time distribution function for the whole series of reactors, obtained from the transfer function of each single CSTR (Stephanopoulos, 1984) by application of van der Laan's theorem (Villermaux, 1976), reads

$$E^{**}_{tot}(t^{**}) = Da_{tot} \sum_{m=1}^{N} \frac{Da_m^{N-2}}{\prod_{\substack{n=1 \\ n \neq m}}^{N} (Da_m - Da_n)} \exp\left\{-\frac{Da_{tot}}{Da_m} t^{**}\right\}, \quad N \geq 2 \quad \ldots\ldots (27)$$

Using the rules of differentiation of an implicit function (Stephenson, 1973), recalling Equation (26), and realizing

TABLE 1

Dimensionless Concentration of Substrate at the Outlet of Each Reactor for the Case of Complete Micromixing, $C^*_{i,cm,opt}$ (first row), and Complete Segregation, $C^*_{i,cs}$ (second row), Under the Assumption that $K^* = 10^{-2}$, $C^*_{N,cm} = 0.100$, and $Da_{i,cs} = Da_{i,cm,opt}$.

| $i$ / $N$ | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1.000 | 0.100 | | | | | | | | | |
| | 1.000 | 0.375 | | | | | | | | | |
| 2 | 1.000 | 0.316 | 0.100 | | | | | | | | |
| | 1.000 | 0.471 | 0.271 | | | | | | | | |
| 3 | 1.000 | 0.464 | 0.215 | 0.100 | | | | | | | |
| | 1.000 | 0.546 | 0.322 | 0.210 | | | | | | | |
| 4 | 1.000 | 0.562 | 0.316 | 0.178 | 0.100 | | | | | | |
| | 1.000 | 0.606 | 0.380 | 0.249 | 0.172 | | | | | | |
| 5 | 1.000 | 0.631 | 0.398 | 0.251 | 0.158 | 0.100 | | | | | |
| | 1.000 | 0.655 | 0.436 | 0.296 | 0.206 | 0.148 | | | | | |
| 6 | 1.000 | 0.681 | 0.464 | 0.316 | 0.215 | 0.147 | 0.100 | | | | |
| | 1.000 | 0.695 | 0.487 | 0.344 | 0.247 | 0.179 | 0.133 | | | | |
| 7 | 1.000 | 0.720 | 0.518 | 0.373 | 0.268 | 0.193 | 0.139 | 0.100 | | | |
| | 1.000 | 0.728 | 0.532 | 0.390 | 0.288 | 0.215 | 0.161 | 0.122 | | | |
| 8 | 1.000 | 0.750 | 0.562 | 0.422 | 0.316 | 0.237 | 0.178 | 0.133 | 0.100 | | |
| | 1.000 | 0.755 | 0.571 | 0.433 | 0.329 | 0.251 | 0.193 | 0.149 | 0.115 | | |
| 9 | 1.000 | 0.774 | 0.599 | 0.464 | 0.359 | 0.278 | 0.215 | 0.167 | 0.129 | 0.100 | |
| | 1.000 | 0.777 | 0.605 | 0.471 | 0.368 | 0.287 | 0.225 | 0.177 | 0.140 | 0.111 | |
| 10 | 1.000 | 0.794 | 0.631 | 0.501 | 0.398 | 0.316 | 0.251 | 0.200 | 0.158 | 0.126 | 0.100 |
| | 1.000 | 0.796 | 0.634 | 0.506 | 0.404 | 0.322 | 0.258 | 0.207 | 0.166 | 0.134 | 0.108 |

TABLE 2

Dimensionless Concentration of Substrate at the Outlet of Each Reactor for the Case of Complete Micromixing, $C^*_{i,cm,opt}$ (first row), and Complete Segregation, $C^*_{i,cs}$ (second row), Under the Assumption that $K^* = 10^{-1}$, $C^*_{N,cm} = 0.100$, and $Da_{i,cs} = Da_{i,cm,opt}$.

| $i$ / $N$ | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1.000 | 0.100 | | | | | | | | | |
| | 1.000 | 0.268 | | | | | | | | | |
| 2 | 1.000 | 0.316 | 0.100 | | | | | | | | |
| | 1.000 | 0.442 | 0.206 | | | | | | | | |
| 3 | 1.000 | 0.464 | 0.215 | 0.100 | | | | | | | |
| | 1.000 | 0.535 | 0.297 | 0.168 | | | | | | | |
| 4 | 1.000 | 0.562 | 0.316 | 0.178 | 0.100 | | | | | | |
| | 1.000 | 0.603 | 0.370 | 0.231 | 0.146 | | | | | | |
| 5 | 1.000 | 0.631 | 0.398 | 0.251 | 0.158 | 0.100 | | | | | |
| | 1.000 | 0.655 | 0.433 | 0.289 | 0.195 | 0.132 | | | | | |
| 6 | 1.000 | 0.681 | 0.464 | 0.316 | 0.215 | 0.147 | 0.100 | | | | |
| | 1.000 | 0.696 | 0.487 | 0.343 | 0.242 | 0.172 | 0.123 | | | | |
| 7 | 1.000 | 0.720 | 0.518 | 0.373 | 0.268 | 0.193 | 0.139 | 0.100 | | | |
| | 1.000 | 0.729 | 0.533 | 0.391 | 0.288 | 0.213 | 0.157 | 0.117 | | | |
| 8 | 1.000 | 0.750 | 0.562 | 0.422 | 0.316 | 0.237 | 0.178 | 0.133 | 0.100 | | |
| | 1.000 | 0.756 | 0.572 | 0.434 | 0.330 | 0.252 | 0.192 | 0.147 | 0.112 | | |
| 9 | 1.000 | 0.774 | 0.599 | 0.464 | 0.359 | 0.278 | 0.215 | 0.167 | 0.129 | 0.100 | |
| | 1.000 | 0.778 | 0.606 | 0.473 | 0.370 | 0.289 | 0.226 | 0.178 | 0.140 | 0.110 | |
| 10 | 1.000 | 0.794 | 0.631 | 0.501 | 0.398 | 0.316 | 0.251 | 0.200 | 0.158 | 0.126 | 0.100 |
| | 1.000 | 0.797 | 0.636 | 0.508 | 0.406 | 0.324 | 0.260 | 0.208 | 0.167 | 0.134 | 0.108 |

that $-(\partial\Phi/\partial Da_{tot})_{C^*_N, Da_i}$ does not grow without limit for finite positive values of $Da_{tot}$, Equation (25) becomes

$$\left\{\frac{\partial\Phi}{\partial Da_i}\right\}_{C^*_N, Da_{tot}} = 0 \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (28)$$

Differentiating the integral term in Equation (26) (Stephenson, 1973) according to Equations (27)–(28), one finds that the optimum loci for $Da_{i,cs,opt}$ are analytically defined by

$$\int_0^\infty \left\{\frac{\partial E^{**}_{tot}}{\partial Da_i}\right\}_{Da_{tot}} C^*_{pf}(\omega)\, d\omega = 0 \quad \ldots\ldots\ldots\ldots \quad (29)$$

The limiting form of Equation (29) for the case of first order kinetics (i.e., $K^* >> C^*$) can be easily found to be

TABLE 3
Values of $C^*_{i,cs,opt}$ (first row), $Da_{i,cs,opt}/C^*_{i-1}$ (second row), and $Da_{i+1,cs,opt}/C^*_{i-1}$ (third row) for a Number of Values of $K^*$ and $C^*_{i+1}/C^*_{i-1}$.

| $K^*$ / $C^*_{i+1}/C^*_{i-1}$ | $10^{-2}$ | $10^{-1}$ | $10^{0}$ | $10^{1}$ | $10^{2}$ |
|---|---|---|---|---|---|
| 0.05 | 0.299 | 0.287 | 0.249 | 0.227 | 0.224 |
| | 1.349 | 1.656 | 4.742 | 36.18 | 348.0 |
| | 0.837 | 1.200 | 4.504 | 35.65 | 347.4 |
| 0.10 | 0.381 | 0.375 | 0.341 | 0.321 | 0.316 |
| | 0.973 | 1.154 | 3.093 | 22.51 | 216.9 |
| | 0.618 | 0.851 | 2.875 | 22.42 | 216.4 |
| 0.15 | 0.445 | 0.437 | 0.409 | 0.391 | 0.387 |
| | 0.773 | 0.919 | 2.347 | 16.61 | 158.8 |
| | 0.520 | 0.677 | 2.146 | 16.39 | 158.4 |
| 0.20 | 0.495 | 0.491 | 0.469 | 0.451 | 0.447 |
| | 0.652 | 0.761 | 1.865 | 13.01 | 124.2 |
| | 0.447 | 0.575 | 1.745 | 12.86 | 123.8 |
| 0.25 | 0.541 | 0.535 | 0.517 | 0.503 | 0.500 |
| | 0.558 | 0.654 | 1.558 | 10.58 | 100.5 |
| | 0.397 | 0.494 | 1.422 | 10.42 | 100.3 |
| 0.30 | 0.579 | 0.575 | 0.563 | 0.551 | 0.548 |
| | 0.491 | 0.570 | 1.311 | 8.745 | 83.03 |
| | 0.350 | 0.431 | 1.204 | 8.648 | 82.81 |
| 0.35 | 0.615 | 0.617 | 0.605 | 0.595 | 0.592 |
| | 0.434 | 0.492 | 1.117 | 7.320 | 69.44 |
| | 0.313 | 0.389 | 1.030 | 7.265 | 69.27 |
| 0.40 | 0.653 | 0.653 | 0.645 | 0.635 | 0.633 |
| | 0.380 | 0.432 | 0.953 | 6.194 | 58.47 |
| | 0.286 | 0.347 | 0.891 | 6.120 | 58.36 |
| 0.45 | 0.685 | 0.683 | 0.679 | 0.673 | 0.671 |
| | 0.337 | 0.385 | 0.828 | 5.248 | 49.40 |
| | 0.256 | 0.303 | 0.760 | 5.182 | 49.29 |
| 0.50 | 0.727 | 0.719 | 0.713 | 0.709 | 0.707 |
| | 0.285 | 0.334 | 0.714 | 4.443 | 41.72 |
| | 0.242 | 0.275 | 0.654 | 4.387 | 41.63 |
| 0.55 | 0.755 | 0.749 | 0.745 | 0.743 | 0.742 |
| | 0.274 | 0.301 | 0.614 | 3.753 | 35.10 |
| | 0.188 | 0.234 | 0.559 | 3.696 | 35.03 |

$$Da_{i,cs,opt,K^* \to \infty} - Da_{i-1,cs,opt,K^* \to \infty} = 0 \quad \ldots\ldots \quad (30)$$

whereas the zero order counterpart (i.e., $K^* << C^*$) takes the form

$$\frac{Da_{i-1,cs,opt,K^* \to 0} - Da_{i,cs,opt,K^* \to 0}}{Da_{i-1,cs,opt,K^* \to 0} - Da_{i,cs,opt,K^* \to 0}} + \frac{2\, Da_{i-1,cs,opt,K^* \to 0}\; Da_{i,cs,opt,K^* \to 0}}{-\,2\, Da_{i-1,cs,opt,K^* \to 0}\; Da_{i,cs,opt,K^* \to 0}} + \exp\left\{\frac{1}{Da_{i,cs,opt,K^* \to 0}} - \frac{1}{Da_{i-1,cs,opt,K^* \to 0}}\right\} = 0 \quad \ldots\ldots \quad (31)$$

The values of the intermediate concentrations leading to the minimum overall space time under the assumption of complete segregation are given in Table 3 for a number of values of $K^*$ and ratios of the consecutive concentrations. The corresponding corrected Damköhler numbers are also included.

## Discussion

In a real fluid there is, in general, partial segregation: it can be considered as a mixture of microfluid and macrofluid (Dunn and Hsu, 1973). However, the characterization of the state of mixing is not a straightforward task. The optimization of the series of CSTR's for each one of the two limiting behaviors of complete segregation and complete micromixing proves, therefore, more useful in the predesign steps of single-phase, isothermal enzymatic reactors than the aforementioned approach. For relatively viscous solutions, or for batches obtained from the addition of two independent fluids requiring long stirring times for complete homogenization, the model based on complete segregation is expected to provide better results than the complete micromixing counterpart.

A careful observation of Figure 1 gives rise to a number of interesting conclusions. For normalized concentrations above, say, 0.7 there is virtually no difference between the complete micromixing and the complete segregation models. This behavior was expected in the neighborhood of nil $Da_i$ as obtained from Equations (18) and (21) coupled with Equations (2) and (23). On the other hand, higher conversions of substrate yield greater differences between the two models, this fact being particularly significant for smaller $K^*$. Therefore, the optimal design obtained from Equation (3) on the assumption of complete micromixing fails for fast biochemical reactions. This feature is emphasized in Tables 1 and 2. The concentrations of substrate that would have been obtained at the outlet of the series of CSTR's using the optimal design suggested elsewhere (Luyben and Tramper, 1982) if the complete segregation model were valid are consistently above the expected concentrations under complete micromixing conditions. This is particularly true for a low number of units and/or a small value for $K^*$. The optimal size of the CSTR series network based on the assumption of complete segregation yields, thus, a more conservative approach than the one obtained by using the complete micromixing model.

The Michaëlis–Menten kinetic equation can be viewed as a kinetic equation of the power-law type provided that a varying order from zero to unity is considered. Since the substrate conversion for reactions with positive order less than unity increases with the degree of micromixing (Bailey and Ollis, 1986), it is expected that the overall space time required to effect a given conversion of substrate under complete segregation be longer than under complete micromixing. Therefore, the actual reactor size required to bring about a given conversion is higher for the complete segregation model than is for the complete micromixing model. As the first-order asymptotic behavior is approached (i.e., large $K^*$), the difference between the two micromixing models disappear (see Figure 1). This fact is also apparent from Equation (20) as compared to the solution of Equation (1) for $K^* + C^*_{i,cm} \sim K^*$. This observation may be justified using the superposition principle for linear systems (Bailey and Ollis, 1986).

The results tabulated in Table 3 show the optimal intermediate concentrations for each set of two consecutive CSTR's with given inlet and outlet concentrations. Equation (14) was used instead of Equation (13) in the calculation of

the normalized substrate concentrations under the segregation assumption because it is numerically much more stable. The range of conversions presented corresponds to the ratios usually found in industrial practice. As expected, larger values for $K^*$ and/or higher conversions give rise to greater Damköhler numbers. Important to note is the fact that the intermediate optimal concentrations under the complete segregation assumption depend on parameter $K^*$ although the same does not hold for the complete micromixing model (Luyben and Tramper, 1982). The optimal intermediate concentrations when $K^*$ tends to infinity approach the concentrations given by Equation (3), and the values for the intermediate Damköhler numbers agree with the result denoted as Equation (30). When $K^*$ approaches zero, the asymptotic zero order behavior leading to Equation (31) is approximatively satisfied as expected.

If only three units are employed, with a known overall conversion of substrate, the optimization may proceed as follows:

(i) arbitrarily select the concentration of solute at the outlet of the second reactor;
(ii) use Table 3 to obtain the optimal concentration at the outlet of the first unit;
(iii) take the value from (ii) together with the final concentration at the outlet of the third unit to obtain a new estimate for the concentration at the outlet of the second reactor;
(iv) compare the two estimates and iterate the process if required until convergence is achieved.

If more than three units are being considered generalization of the foregoing process is extremely tedious, as is the direct employment of Equation (29).

An alternative, yet more suitable approach for higher number of reactors can be devised as follows:

(i) compute $C^*_{i,cs,opt,K^* \to \infty}$ using Equation (3);
(ii) obtain $Da_{i,cs,opt,K^* \to \infty}$ from Equation (1);
(iii) arbitrarily select $C^*_{1,cs,opt,K^* \to 0}$, and obtain $Da_{1,cs,opt,K^* \to 0}$ from Equation (17);
(iv) obtain $Da_{i,cs,opt,K^* \to 0}$ for every $i = 2, 3, \ldots, N$ taking advantage of Equation (31), and compute $C_{i,cs,opt,K^* \to 0}$ using Equation (17) again;
(v) compare $C^*_{N,cs,opt,K^* \to 0}$ with $C^*_N$, and iterate from (iii) if required;
(vi) once in possession of the asymptotic limits for the normalized concentrations, implement a numerical algorithm aimed at the multivariate nonlinear minimization of $Da_{tot,cs}$ constrained by the fact that $C^*_{N,cs,opt} = C^*_N$ (see Gill et al., 1981; Bard, 1974). The result given by the reciprocal of Equation (23) may be used to advantage to determine the steepest descent direction and the step size on the basis of the definition of $Da_{tot,cs}$ as the sum of all Damköhler numbers for the reactor network.

## Nomenclature

$C$ = concentration of substrate (mol · m$^{-3}$)
$C^*$ = $(C/C_o)$, normalized concentration of substrate
$Da$ = $(\nu_m \tau / C_o)$, Damköhler number associated with the reactor
$E$ = residence time distribution density function (s$^{-1}$)
$E^*$ = $(E \cdot \tau_i)$, normalized residence time distribution assuming each reactor independently
$E^{**}$ = $(E \cdot \tau_{tot})$, normalized residence time distribution assuming all reactors at the same time
$Er$ = relative error
$H$ = Heaviside step function
$K$ = kinetic constant (mol · m$^{-3}$)
$K^*$ = $(K_m/C_o)$, dimensionless kinetic constant
$L$ = length of plug flow reactor (m)
$m$ = dummy integer variable
$n$ = dummy integer variable
$N$ = number of CSTR's in the reactor network
$Q$ = volumetric flow rate of fluid through the CSTR's (m$^3$ · s$^{-1}$)
$t$ = residence time of fluid element (s)
$t^*$ = $(t/\tau_i)$, normalized residence time of fluid element
$t^{**}$ = $(t/\tau_{tot})$, normalized residence time of fluid element
$u$ = axial velocity of fluid in plug flow reactor (m · s$^{-1}$)
$V$ = volume occupied by the reacting mixture (m$^3$)
$v$ = maximum reaction rate (mol · m$^{-3}$ · s$^{-1}$)

### *Greek letters*

$\Gamma$ = gamma function
$\zeta$ = dummy variable of integration (using normalized concentration values as the limits of integration)
$\xi$ = dummy variable of integration (using normalized time values, $t^*$, as the limits of integration)
$\sigma$ = $[t/(L/u)]$, elapsed time normalized by the space time of plug flow reactor
$\tau$ = $(V/Q)$, space time of CSTR (s)
$\Phi$ = auxiliary implicit function of $\tau_i$ $(i = 1,2,\ldots,N)$ and $C^*_N$
$\omega$ = dummy variable of integration (using normalized time values, $t^{**}$, as the limits of integration)

### *Subscripts*

*1%* = leading to an absolute fractional error below 1%
*cm* = under the assumption of complete micromixing in the liquid phase
*cs* = under the assumption of complete segregation in the liquid phase
*i* = referring to the $i$-th CSTR in the series
$K^* \to 0$ = when $K^*$ approaches zero
$K^* \to \infty$ = when $K^*$ approaches infinity
$K^*/Da_i \to 0$ = when $K^*/Da_i$ approaches zero
$K^*/Da_i \to \infty$ = when $K^*/Da_i$ approaches infinity
*m* = referring to the Michaëlis-Menten kinetic equation
*max* = referring to the last term of the power series before truncature
*o* = referring to the inlet stream of the first CSTR in the series
*opt* = leading to a minimum overall space time for the series of CSTR's
*pf* = referring to a plug flow reactor
*tot* = referring to the overall CSTR network

## References


Arima, K., in "Global Impacts of Applied Microbiology", M. P. Starr, Ed., John Wiley and Sons, New York (1964), p. 278.
Aris, R., "The Optimal Design of Chemical Reactors", Academic Press, New York (1961).
Bailey, J. E. and D. F. Ollis, "Biochemical Engineering Fundamentals", McGraw-Hill Book Co., New York (1986).
Bard, Y., "Nonlinear Parameter Estimation", Academic Press, New York (1974).

Beyer, W. H., Ed., 'CRC Standard Mathematical Tables'', CRC Press, Boca Raton (1978).
Bischoff, K. B., ''Optimal Continuous Fermentation Reactor Design'', Can. J. Chem. Eng. **44**, 281–284 (1966).
Danckwerts, P. V., ''Continuous Flow Systems: Distribution of Residence Times'', Chem. Eng. Sci. **2**, 1–13 (1953).
Dunn, R. and C. Hsu, ''A Generalized Mixing History Model of an Imperfectly Mixed Reactor'', Can. J. Chem. Eng. **51**, 378–380 (1973).
Gill, P. E., W. Murray and M. H. Wright, ''Practical Optimization'', Academic Press, New York (1981).
Hill, C. G., ''An Introduction to Chemical Engineering Kinetics and Reactor Design'', John Wiley and Sons, New York (1977).
Kreyszig, E., ''Advanced Engineering Mathematics'', John Wiley and Sons, New York (1979).
Levenspiel, O., ''Chemical Reaction Engineering'', John Wiley and Sons, New York (1972).
Luyben, K. C. and J. Tramper, ''Optimal Design for Continuous Stirred Tank Reactors in Series Using Michaëlis-Menten Kinetics'', Biotechnol. Bioeng. **24**, 1217–1220 (1982).
Malcata, F. X., ''HERSIM: a Microcomputer Program Designed to Compute the Limits of Conversion for Real Homogeneous Isothermal Enzymic Reactors'', CABIOS **3**, 105–109 (1987).
Malcata, F. X., ''Optimal Design on an Economic Basis for Continuous Stirred Tank Reactors in Series Using Michaëlis-Menten Kinetics for Ping-Pong Reactions'', Can. J. Chem. Eng. **66**, 168–172 (1988).
Malcata, F. X., ''A Heuristic Approach for the Economic Optimization of a Series of CSTR's Performing Michaëlis-Menten Reactions'', Biotechnol. Bioeng. **33**, 251–255 (1989a).
Malcata, F. X., ''CSTR's in Biochemical Reactions — an Optimization Problem'', Chem. Eng. Ed. **23**, 112–115, 128 (1989b).
Spiegel, M. R., ''Mathematical Handbook'', McGraw-Hill Book Co., New York (1968).
Stephanopoulos, G., ''Chemical Process Control — an Introduction to Theory and Practice'', Prentice-Hall, Englewood Cliffs, NJ (1984).
Stephenson, G., ''Mathematical Methods for Science Students'', Longman, London (1973).
Villermaux, J., ''Génie de la Réaction Chimique'', Technique et Documentation Lavoisier, Paris (1976).
Zwietering, Th. N., ''The Degree of Mixing in Continuous Flow Systems'', Chem. Eng. Sci. **9**, 1–15 (1959).